Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: Consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases

Chapple, Iain

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Complete List of Authors:	Chapple, Iain; The University of Birmingham, Periodontal Research Group; Schulte, Andreas; University of Heidelberg, Department of Conservative Dentistry BOUCHARD, Philippe; U.F.R. d'Odontologie Université Paris 7, Periodontology Cagetti, Maria Grazia; WHO Collaboration Centre for Epidemiology and Community Dentistry, Campus, Guglielmo; Universita degli Studi di Sassari, Department od Surgery, Microsurgery and Medicine Sciences, School of Dentistry; WHO Collaboration Centre for Epidemiology and Community Dentistry, Carra, Maria Clotilde; Rothschild Hospital, Departement of Periodontology Cocco, Fabio; Universita degli Studi di Sassari, Department od Surgery, Microsurgery and Medicine Sciences, School of Dentistry NIBALI, LUIGI; Eastman Dental Institute and Hospital, University College London, Periodontology Unit and Division of Clinical Research Hujoel, Philippe; University of Washington, Public Health Sciencesriodontology; Laine, Marja; Academic Centre for Dentistry in Amsterdam, Department of Periodontology Lingström, Peter; Institute of Odontology, Department of Cariology Manton, David; University of Melbourne, Melbourne Dental School; Montero, Eduardo; Universidad Complutense de Madrid, Faculy of Dentistry Pitts, Nigel; Kings College London, School of Dentistry Range, Helene; Service of Odontology, Garancière Rothschild Hospital, AP-HP, Paris 7-Denis Diderot University, U.F.R. of Odontology, Department of Periodontology Schulter, Nadine; Albert-Ludwigs-Universitat Freiburg, Division for Cariology, Dept. of Operative Dentistry and Periodontology Teughels, Wim; K. U. Leuven, Periodontology Twetman, Svante; University of Copenhagen, Section of Cariology, School of Dentistry, Faculty of Health Science Loveren, Cor ; Academic Centre for Dentistry Amsterdam, Cariology Van der Weijden, G.A.; Academic Centre for Dentistry Amsterdam, Periodontology Vieira, Alexandre R.; University of Pittsburgh, Oral Biology

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Chapple, Iain L.C. UK (Chairman)
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Twetman, Svante. Denmark
Van Loveren, Cor. Netherlands
Van der Weijden, Fridus, Netherlands
Vieira, Alexandre, R. USA

Sponsor Representatives

Michael Schneider (Colgate)

Running head: Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases.

Key words: caries, periodontal diseases, gingivitis, periodontitis, risk factor, prediction factor, prognostic factor, acquired risk factors, genetics, genome wide association study (GWAS), candidate gene study (CGS), single nucleotide polymorphism (SNP), vitamin D receptor (*VDR)* gene, Fc gamma receptor IIA (*FcγRIIA)* gene, Interleukin 10 (*IL10*) gene, amelogenin (*AMELX*) gene, aquaporin (*AQP5*) gene, micronutrient, macronutrient, vitamin C, vitamin D, vitamin B12, carbohydrate, polyunsaturated fatty acid (PUFA), protein, malnutrition, diet, nutrition, sugars, starch, fluoride, saliva, gingival bleeding, oral hygiene frequency, smoking, diabetes, hyposalivation.

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ABSTRACT

Periodontal diseases and dental caries are the most common diseases of humans and the main cause of tooth loss. Both diseases can lead to nutritional compromise and negative impacts upon self-esteem and quality of life. As complex chronic diseases, they share common risk factors, such as a requirement for a pathogenic plaque biofilm, yet they exhibit distinct pathophysiology's. Multiple exposures contribute to their causal pathways, and susceptibility involves risk factors that are inherited (e.g. genetic variants), and those that are acquired (e.g. socio-economic factors, biofilm load or composition, smoking, carbohydrate intake). Identification of these factors is crucial in the prevention of both diseases as well as in their management.

Aim: To systematically appraise the scientific literature to identify potential risk factors for caries and periodontal diseases.

Methods: One systematic review (genetic risk factors), one narrative review (role of diet and nutrition) and reference documentation for modifiable acquired risk factors common to both disease groups, formed the basis of the report.

Results: There is moderately strong evidence for a genetic contribution to periodontal diseases and caries susceptibility, with an attributable risk estimated to be up to 50%. The genetics literature for periodontal disease is more substantial than for caries and genes associated with chronic periodontitis are the vitamin D receptor (*VDR*), Fc gamma receptor IIA (*Fc-γRIIA*) and Interleukin 10 (*IL10*) genes. For caries, genes involved in enamel formation (*AMELX, AMBN, ENAM, TUFT, MMP20*, and *KLK4)*, salivary characteristics (*AQP5*), immune regulation and dietary preferences had the largest impact. No common genetic variants were found. Fermentable carbohydrates (sugars and starches) were the most relevant common dietary risk factor for both diseases, but associated mechanisms differed. In caries, the fermentation process leads to acid production and the generation of biofilm components such as Glucans. In periodontitis, glycaemia drives oxidative stress and advanced glycation end-products may also trigger a hyper inflammatory state. Micronutrient deficiencies, such as for vitamin C, vitamin D or vitamin B12, may be related to the onset and progression of both diseases. Functional foods or probiotics could be helpful in caries prevention and periodontal disease management, although evidence is limited and biological mechanisms not fully elucidated. Hypo-salivation, rheumatoid arthritis, smoking/tobacco use, undiagnosed or sub-optimally controlled diabetes and obesity are common acquired risk factors for both caries and periodontal diseases.

Inherited and acquired risk factors for dental caries and periodontal diseases

Periodontal diseases and dental caries are complex diseases with multiple and diverse exposures that impact upon risk of disease initiation (risk factors) or progression of existing disease (prognostic factors). Exposures include those that are inherited (e.g. genetic variants), those that are acquired, such as social, educational and economic factors, and the local environment (e.g. biofilm load or composition), other diseases (e.g. sub-optimally controlled diabetes) and lifestyle (e.g. smoking, consumption of sugars, carbohydrate intake) factors. These may arise in different combinations in different individuals, and at an individual patient level may also have differentially weighted effects.

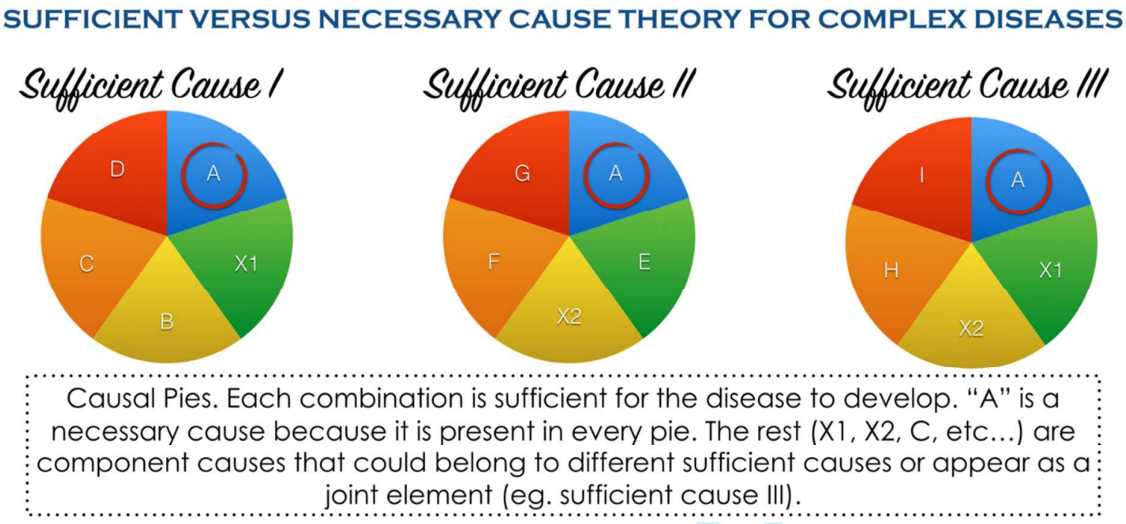
In this consensus report, periodontal diseases are regarded as biofilm-initiated inflammatory conditions, principally gingivitis and periodontitis. Globally, periodontitis affects between 45% and 50% of adults in its mildest form and the most severe disease impacts upon 9%-11% of the world's adult population (Eke et al., 2012, Kassebaum et al., 2014, Jepsen et al., 2016). In periodontal health there is a symbiosis between a health-associated biofilm and a proportionate host immune-inflammatory response. Periodontitis develops following the emergence of a dysbiosis in susceptible individuals which is associated with dysregulation of the immune-inflammatory response, and which leads to host-mediated connective tissue damage and alveolar bone loss (Meyle & Chapple 2015, Mira et al., 2016, Sanz et al., 2017).

In this report the term dental caries encompasses the process of the disease as well as lesion severity and extent (initial, moderate and extensive), active or inactive lesions and anatomical location (coronal and root caries) in both primary and permanent dentitions. Caries involves interactions between the tooth structure, the biofilm formed on the tooth surface, sugars and salivary and genetic factors (Pitts & Zero 2016). Caries is prevalent at all ages with peaks of untreated cavitated dentinal caries at 6, 26 and 70-years (Kassebaum 2015, Jepsen et al., 2016). Untreated cavitated caries in the permanent dentition was the most prevalent condition evaluated for the entire Global Burden of Diseases 2010 Study, with a global prevalence of 2,431,636 (35%) for all ages combined (Marcenes et al., 2013).

The outcome of both diseases if left untreated may be tooth loss, reduced masticatory function, poorer nutritional status, low self-esteem and quality of life, negative general health impacts. There is also evidence of an association with higher all-cause mortality (Garcia et al., 1998, Kim et al., 2013).

Traditional terminology employed by some in risk factor research can cause confusion. For example, the term "putative" risk factor or "risk indicator" implies that an exposure is independently associated with a disease but that longitudinal (temporal) data may not be available to substantiate the strength and directionality of the relationship. Risk or prognostic factors do not have to be component causes of a

disease. To avoid confusion and for the purposes of this consensus the set of causes that initiate chronic diseases such as caries and periodontal diseases should be referred to as “sufficient causes” (Rothman, 2002). Disease is thus not caused by a single factor and multiple sufficient causes are typically responsible for a given disease. A component cause, which is an element of all the sufficient causes for a given disease, is referred to as a necessary cause (e.g. “A” in Figure). Interaction between two component causes X1 and X2 is present when component cause X1 belongs to one sufficient cause, component cause X2 belongs to another sufficient cause, and X1 and X2 are jointly an element of a third sufficient cause (Figure adapted from Rothman, 2002). Any factor that is associated with an increased probability of disease onset is referred to as a risk factor. A prognostic factor may be a subset of risk factors which refers to patient-specific demographic, disease characteristics, or co-morbid conditions affecting the likelihood of an outcome.



Causal Pies. Each combination is sufficient for the disease to develop. “A” is a necessary cause because it is present in every pie. The rest (X1, X2, C, etc…) are component causes that could belong to different sufficient causes or appear as a joint element (eg. sufficient cause III).

Being complex diseases where multiple exposures may contribute to their causal pathways, the correction of one risk factor may not lead to disease cure. It is important to state that increased risk does not necessarily imply causation, as certain factors may increase susceptibility to a disease developing but may not fulfil all the requirements required for a causal factor. For this, temporal associations between the risk factor and disease onset should be established, with the risk factor arising prior to the disease onset; the risk factor also being associated with an increased frequency of the disease within a population; biological mechanistic plausibility regarding how the risk factor may contribute to disease onset; and evidence that risk factor management leads to improvement in the disease or its resolution (Hill, 1971).

The purpose of this consensus report is to define common risk factors for caries and periodontal diseases that impact upon the incidence, progression or indeed re-activation of treated disease, with a view to developing age-orientated guidelines for patients, practitioners and public health authorities. For the questions set in this report, common risk factors covered elsewhere in the workshop (e.g. Jepsen et al.,

2017) such as those relating to oral hygiene, biofilm, social, educational and economic factors, and fluoride were excluded. The longer-term goal is to help to reduce the prevalence of these two common oral diseases by informing the public and profession on risk factors that are related to caries and periodontal diseases, thereby reducing the human and health economic burden of these ubiquitous human diseases.

This report represents the consensus views of Working Group 2 of the 1st joint European Workshop on Periodontal diseases and Dental Caries. It is substantially, but not entirely, based upon one systematic review of the available and published evidence relating to genetic risk factors for periodontal diseases and caries (Nibali et al., 2017), one narrative review on the role of diet and nutrition in development and progression of periodontal diseases and caries (Hujoel & Lingström 2017), and reference documentation provided on common modifiable risk factors common to both disease groups.

The role of host genetics in the pathogenesis of periodontal diseases and caries

Is there evidence that genetic factors play a role in periodontal diseases or caries? If so what is the likely magnitude of the impact upon risk?

Evidence for the role of genetic factors in periodontal diseases initially emerged from familial aggregation studies (Saxen et al., 1980, van der Velden et al., 1993) and from studies of twins reared together and apart (Michalowicz et al 1991). Similarly, the evidence for a genetic basis of caries susceptibility arose from family and twin studies (Klein and Palmer 1940, Boraas et al., 1988, Conry et al., 1993) and was complemented by animal studies (Hunt et al., 1944, Rosen et al., 1961).

Research over the last two decades has focused on gene mapping (Hart et al., 1993) and identification of specific genetic variants predisposing to periodontitis (Kornman et al., 1997). A similar approach has been employed for caries over the last decade (Vieira et al., 2008).

The current understanding is that with the exception of rare single-gene forms of disease (Hart & Atkinson, 2007, Tucker et al., 2007) susceptibility to periodontal diseases and caries is polygenic in nature (Kinane et al., 2005, Laine et al., 2012, Vieira et al., 2014, Nibali et al., 2017).

The magnitude of genetic contribution to both diseases has been estimated in monozygotic and dizygotic twin studies (Booras et al., 1988, Michalowicz et al., 1991). Heritability of caries has been calculated for a number of caries surrogate measures (i.e. mandibular right first molar loss, presence of untreated lesions, number of affected occlusal surfaces, depth of dentinal lesions, preference for

sugars, presence of specific microbial species) and varies from 26% to 64% (Nibali et al., 2017). The magnitude of a genetic contribution to overall periodontitis susceptibility (measured clinically or self-reported) has been estimated as 33% to 50% (Michalowicz et al., 1991, 2000, Mucci et al., 2005). The increase in odds for individual genetic variants based on robust association studies on periodontal diseases and caries is estimated to be up to 50% (Nibali et al., 2017).

Therefore, the available data support at least a moderate role for a genetic component cause to periodontal diseases and to caries susceptibility. Genetic risk is subsequently modified by lifestyle (acquired) and environmental factors.

Is there evidence from candidate gene studies (CGS) and genome wide association studies (GWAS) that particular gene variants may be associated with periodontal diseases and are these associations consistent across different populations?

Sixty papers were evaluated in a systematic review (including large CGS, GWAS and systematic reviews involving different populations) (Nibali et al., 2017). Criteria employed to assess the strength of the evidence were based on the quality of the evidence and replication of findings across different studies. Given the inclusion criteria applied, no specific studies were found on genetic susceptibility to gingivitis. Three genes emerged with a strong level of evidence for association with chronic periodontitis. These were vitamin D receptor (*VDR*), Fc gamma receptor IIA (*Fc-γRIIA*) and Interleukin 10 (*IL10*). However, these associations were often observed for different gene variants and/or in different populations. For other gene variants weak to moderate evidence emerged with respect to an association with chronic periodontitis as well as aggressive periodontitis (Nibali et al., 2017). It seems clear that different genetic variants may modulate disease susceptibility in different geographic origins.

Additional research is required to clarify the mechanisms underlying these genetic associations and their functional relevance to the pathogenesis of periodontal diseases. There is emerging evidence for a role of host genetic variants on subgingival microbial colonization, which needs to be explored further (Divaris et al., 2012, Nibali et al., 2017).

Is there evidence from candidate gene studies (CGS) and genome-wide association studies (GWAS) that particular gene variants may be associated with caries and are these associations consistent across different populations?

Some common gene variants appear to confer caries susceptibility in both primary and permanent dentitions. Some also appear to be dentition specific, which likely

reflects the known anatomical/structural differences between both dentitions (Bayram et al., 2015).

Current evidence from independently replicated results in multiple populations suggests that those genes with the largest impact on caries susceptibility are involved in enamel formation, immune regulation, salivary function, and dietary preferences (Nibali et al., 2017). The most important genes involved in enamel formation to date have been identified as *AMELX, AMBN, ENAM, TUFT, MMP20*, and *KLK4*. Genes determining dietary preferences include *TAS2R38* and *TAS1R2*. *LTF* has been identified as impacting upon host immune responses. *AQP5* is a gene that influences salivary characteristics (Nibali et al., 2017).

In addition, the original genome-wide linkage study for caries in cohorts from multiple populations has successfully fine-mapped at least three loci, which contain *ESRRB, BTF3*, and *TRAV4*. The results from the GWAS are yet to be independently confirmed (Nibali et al., 2017).

Are there common gene variants that predispose to both periodontal diseases and caries?

Pleiotropy (one gene appearing to affect two or more un-related phenotypic traits) in periodontal diseases and caries may exist. Both diseases are bacterially-initiated, therefore logic dictates that common immune-regulating genes may modulate susceptibility to both diseases. Some independent studies have revealed limited evidence for associations between certain genes and their variants with both diseases (e.g. *DEFB1, CD14* and HLA locus) (Nibali et al., 2017). Furthermore, genetic influences on human behaviour may play an important role in both periodontal diseases and caries.

However, cross-checking genes associated with periodontitis with those associated with caries revealed no conclusive evidence for gene variants common to both diseases (Nibali et al., 2017). This may also reflect limitations in thebe a reflection of inconsistency of disease definitions, the insufficient power of individual studies, or limitations due to the inclusion criteria employed within the review. Only one of the reviewed included studies in the review investigated common genetic factors for both periodontitis and caries in the same study group, and reported no common associations (Öztürk et al., 2010). It is important to mention that different pathogenic pathways clearly exist despite some overlap between these two diseases. Despite some overlap when it relates relative to genetic contributions, complete overlap cannot be expected, since. different pathogenic pathways clearly exist. *LTF* is an example of potential antagonistic pleiotropy is *LTF* which is, suggested to be protective for caries but predisposing to localised aggressive periodontitis (Fine, 2015).

Due to rapid rates of discovery in the field of genetics research, analysis of pleiotropy between both diseases should be regularly repeated to unveil studies attempting to unveil the mechanisms underlying genetic associations. More specific phenotypic definitions for periodontal diseases and caries should be employed in research on the role of gene variants, including gene expression and other mechanisms of controlling gene function (epigenetics).

Diet, nutrition, dental caries, and periodontal diseases

Is dental caries related to diet? If so what are the most important dietary risk factors?

Based on over 100 years of research, there is unequivocal evidence that dietary fermentable carbohydrates (sugars, starch) are a necessary cause, but alone, not a sufficient cause for caries initiation and progression. Differences in the cariogenic potential of distinct carbohydrates exist, despite the presence of only small variations seen in biofilm acidogenicity. In this respect sucrose deserves special attention due to the fact that apart from being rapidly converted into acid it can also be synthesised into extracellular glucans, fructans and intracellular storage compounds. The cariogenic potential of starch varies greatly due to the variation in bioavailability of starches within processed foods. Concentration and bioavailability of carbohydrates within foods and composition as well as adhesiveness of the diet, are additional influencing factors (Lingström et al., 2000, Zero, 2004).

Behavioural factors may influence whether disease develops or not. Frequency of carbohydrate intake and physiological factors such as oral clearance, biofilm composition and saliva buffering capacity have received particular attention over time. There is moderate evidence that a diet in which sugars contribute to <10% (50 g/day) of total diet-derived energy (E) is associated with lower caries experience. Whilst the evidence is of low certainty, there are indications that a significant relationship may exist between sugar intake and caries even when free-sugar intake is <5% E (25 g/day) (Moynihan & Kelly, 2014). The working group supports a goal of eliminating sugars from modern diets, but recognises that it will be challenging even to reduce daily levels of intake to 25-50 g/day where a diet contains 2000 calories per day, due to the free-sugars added by manufacturers as mono- and disaccharides in foods and beverages, or due to sugars naturally present in honey, syrups, fruit juices and fruit juice concentrate (WHO, 2015).

Since “nutrition” acts both locally and systemically, lack of dietary micronutrients such as vitamin D, calcium, phosphates and vitamin K, has a negative impact upon tooth mineralisation and tooth quality and size, and may also affect caries risk later in life through other mechanisms (Alvarez, 1995, Southward, 2015, Hujoel, 2013).

It is important to recognise that given the current strong evidence base, RCT’s investigating the impact of frequency, quantity and duration of dietary fermentable

carbohydrate exposure on caries initiation and progression would be unethical to perform.

Are periodontal diseases related to diet? If so what are the most important dietary risk factors?

There is evidence from association studies and controlled clinical depletion studies that periodontal diseases are influenced by diet. Micronutrient deficiencies have been shown to be inversely related to periodontal health. Several studies in different populations have shown an independent inverse association between dietary vitamin C intake and plasma vitamin C concentrations and periodontitis prevalence at a population level, even after adjusting for confounding factors (Van der Velden et al., 2011). Moreover, it has been shown that vitamin C depletion can lead to profuse gingival bleeding (Jacob et al., 1987, Leggott et al., 1986, 1991). Lower serum magnesium/calcium levels, lower antioxidant micronutrient levels, and lower docohexanoic acid intake have also been shown to significantly correlate with higher levels of periodontal diseases (Meisel et al., 2005, Iwasaki et al., 2010, Van der Velden et al., 2011). Whilst there is conflicting evidence relating to vitamin D intake and serum levels to periodontal health (Van der Velden et al., 2011), vitamin D supplementation combined with calcium has been shown to reduce tooth loss and improve periodontal health (Krall et al., 2001, Miley et al., 2009). At a macronutrient level, emerging evidence indicates that a carbohydrate rich diet increases the risk of inflammation and thus gingival bleeding (Hujoel, 2009, Woelber et al., 2016), whereas a switch to a Palaeolithic diet, results in a decrease of gingival bleeding (Baumgartner et al., 2009).

Are there common dietary risk factors for caries and periodontal diseases? If so which factors are most relevant?

Taking into consideration that the mechanisms might be different for both diseases, fermentable carbohydrates are the most relevant common dietary risk factors for caries and periodontal diseases (Moynihan & Petersen 2004). For caries it is primarily related to the fermentation process, which takes place in the dental biofilm during which subsequent acids are formed. For periodontal diseases the most likely biological mechanism involves glucose and advanced glycation end-products triggering a hyper inflammatory state in leukocytes (Van der Velden et al., 2011).

There is also evidence demonstrating that micronutrient deficiencies may influence both diseases at different stages in life. There is evidence that vitamin D deficiency may result in enamel hypoplasia/hypomineralisation, which in turn may result in an increased risk for caries (Hujoel, 2013). Vitamin D deficiency has been associated with periodontitis in cross-sectional studies. A systematic review of randomised trials has suggested that Vitamin B6 supplementation decreases caries experience (Salam et al., 2015).

For periodontal diseases, the result of a cohort study indicated that vitamin B12 deficiency was associated with periodontal disease progression and destruction (Zong et al., 2016).

Do dietary risk factors for periodontal diseases and caries vary across the life course?

Susceptibility to caries varies substantially throughout the life course. Dietary patterns accross the life course change particularly in relation to exposure to the intake of specific fermentable carbohydrates. The increase in caries incidence is correlated with frequency of sugar consumption (EFSA, 2010) and also varies in relation to sugar intake patterns.

Caries risk is particularly high in the young during the early post-eruptive years of the primary and permanent dentition (Carlos & Gittelsohn 1965). Early childhood caries may arise due to incorrect feeding habits (increased sugar exposure during weaning, bottle feeding or prolonged nocturnal breast-feeding) (Avila et al., 2015, Tham et al., 2015). Higher intake of sweets and soft drinks during adolescence increases caries risk. Whilst the evidence is weak, an increased risk may be seen for adults in relation to different working environments (restaurants, food laboratories and shift workers). Following retirement, dietary habits may also change and move towards softer diets with higher sugar intake. Starches are considered a risk factor for caries in root surfaces, which is of particular concern in older people (Lingström et al., 2000).

Caries risk may increase in any age group in relation to physiological changes such as decreased absorption of nutrients, and reduced masticatory function and change is associated with increased use of medications (Zaura & ten Cate 2015). Today dietary recommendations are provided frequently to complement traditional medical therapies. As energy requirements decrease with age, and dietary intake is thus reduced, the risk of micronutrient deficiency may arise (Moynihan, 2007). It is important to ensure that diets, particularly in frail and dependent older people, remain of optimal quality to support disease prevention.

At the present time the impact of dietary risk factors upon periodontal diseases across the course of life remains unclear (van der Putten et al., 2009).

Can caries and periodontal diseases be prevented or treated by dietary interventions?

Due to the dietary-induced origin of dental caries, dietary intervention is considered one of the main strategies for disease prevention. Initial carious lesions may be arrested by dietary intervention (Mellanby et al., 1924, Mellanby & Pattison 1928, Bunting et al., 1933).

The majority of individuals are at risk of caries and periodontal diseases and should thus aim to reduce or eliminate sugar intake. It is particularly important to introduce good dietary habits from birth and to refrain from sugar containing foods. For those at increased risk of disease, additional dietary advice with a focus on intake of sugars should be provided. It is important that both frequency and amount of intake are considered to decrease the risk of root caries. For individuals with exposed root surfaces, a reduction in the intake of starch needs to be considered.

The available evidence on the effects of dietary interventions in a dental setting has shown that there is limited or even no efficacy on caries experience, which is explained mainly by the lack of compliance (Harris et al., 2012).

There is evidence that both caries and periodontal diseases can be influenced by nutritional interventions like vitamin D supplementation and the use of antioxidant micronutrients in patients (Van der Velden et al., 2011).

Apart from sugar restriction, other dietary interventions to prevent caries include sugar substitutes, the recommendation of functional foods and probiotics. For periodontal diseases functional foods may be of particular interest. Recent studies have shown improved clinical outcomes following the adjunctive ingestion of fruit and vegetable extracts (Chapple et al., 2012) and probiotics (Martin-Cabezas et al., 2016). For many of these new strategies, the evidence base remains weak.

Shared acquired risk factors for dental caries and periodontal diseases

What are the acquired risk factors for caries across the life course, other than diet?

The evidence relating to acquired risk factors for caries is derived predominantly from studies in children and relates to hypo-salivation, smoking and medical conditions.

Hypo-salivation: Increased risk of caries initiation and progression is seen in Sjögren's syndrome and rheumatoid arthritis but the level of the underpinning evidence is determined to be very low. Medication and radiation therapy may have side effects that are associated with a higher risk of caries initiation and progression. However, the level of certainty for some anti-depressants and the drug methadone is very low. Also, the level of evidence for radiation therapy is estimated to be low.

Smoking: Exposure to smoke has been associated with caries in several studies, with mechanisms relating to alterations in saliva (Benedetti et al., 2013). Emerging evidence suggests that children's caries experience during their first 4 years of life is significantly increased with mothers who smoke compared to that had a mother who did not smoke (Bernabé et al., 2016).

Medical conditions: There is evidence, albeit at a low level of certainty, that individuals with undiagnosed or sub-optimally controlled type 1 diabetes have an increased risk of caries initiation and progression (Novotna et al., 2015). Children, adolescents and the elderly and those with cognitive impairment that results in limiting behaviours also have an increased risk of caries initiation and progression (certainty very low).

What are the acquired risk factors across the life course for periodontal diseases, other than diet?

The evidence for acquired risk factors for periodontal diseases is predominantly based upon studies in adults and includes cardio-metabolic disorders, rheumatic diseases, hormonal changes in females, risks related to use of medications and exposures arising from addictive behaviours.

Cardio-metabolic disorders: there is a high level of evidence that adults with undiagnosed or sub-optimally controlled diabetes have an increased risk of gingivitis and periodontitis, for which dose-response relationships have been established between levels of glycaemia and periodontal disease risk (Lamster et al., 2014; Eke et al., 2016; Taylor et al., 2013). There is a moderate certainty of evidence that individuals who are obese or overweight and those with the metabolic syndrome have a higher risk of both gingivitis and periodontitis (Keller et al., 2015, Gaio et al., 2016, Nibali et al., 2013, Range et al., 2013). Patients with obstructive sleep apnoea and other sleep disorders have an enhanced risk of periodontal diseases, however, the level of certainty is low (Carra et al., 2016, Lee et al., 2014, Keller et al., 2013, Sanders et al., 2015).

Rheumatic diseases: individuals with rheumatoid arthritis have an increased risk of gingivitis and periodontitis (certainty low) and those with Sjögren's syndrome appear to experience higher levels of periodontal diseases (certainty very low) (Fuggle et al., 2016, Eriksson et al., 2016, Antoniazzi et al., 2009, Le Gall et al., 2016).

Hormonal changes in females: there is a moderate level of evidence that pregnancy imparts an increased risk for periodontal diseases in females. Puberty and the menopause are associated with a higher prevalence of periodontal diseases in females (certainty low) (Mariotti & Mawhinney 2013, Armitage, 2013).

Medications: medications that reduce salivary flow are associated with an increased incidence of periodontal diseases (certainty low to very low). Drugs that induce gingival overgrowth also appear to increase risk of periodontal diseases (certainty moderate) (Heasman & Hughes 2014, Villa et al., 2015).

Tobacco use: there is an increased risk of periodontitis in those individuals who use tobacco, irrespective of the type of tobacco consumption and studies consistently report a dose response for periodontitis risk (certainty high) (Genco & Borgnakke 2013, Nociti et al., 2015, Palmer et al., 2005).

Are there acquired risk factors that are common to caries and periodontal diseases, other than diet?

Based upon current evidence there appear to be five acquired risk factors that are common to both caries and periodontal diseases: hypo-salivation, rheumatoid arthritis, smoking/tobacco use, undiagnosed or sub-optimally controlled diabetes and obesity. Based upon expert opinion, tobacco use and hypo-salivation are important factors to address. These exposures should therefore be targeted in public health campaigns in order to reduce their impact upon these common oral diseases.

Are the common acquired risk factors for periodontal diseases and caries modifiable?

Hypo-salivation, where related to medication use, may be modified by drug substitution in certain situations, however, where hypo-salivation is linked to ageing or physiological impairment, this risk factor may not be modifiable.

Direct exposure to tobacco through personal habits can and should be modifiable, however, exposure via environmental smoke may be challenging to address.

Recommendations for future research

In order to advance understanding of the role played by genetics in caries and periodontal disease initiation and/or progression, further research is required to address the issues below:

- Develop clear definitions of disease in order to facilitate the identification of individuals that are at the highest risk for the development of the disease;
- Conduct studies that are sufficiently powered;
- Undertake studies that employ longitudinal designs to better inform questions around causality;
- Conduct research in diverse populations of different geographical origins and different age groups;
- Design hypothesis driven (candidate gene) or hypothesis free (GWAS) studies of caries and periodontal diseases within the same population cohorts and take into account interaction between different factors;
- Attempts to unravel the mechanisms underlying genetic associations should be undertaken in search of the role of gene variants including gene expression and other mechanisms of controlling gene function (epigenetics).
- In genetics studies that report low p-values but have employed small sample sizes should clearly state their limitations regarding a low “strength” of association due to low study power, or similarly, they should not conclusively exclude potential gene associations.

Acquired risk factors common to caries and periodontal diseases

- Undertake research designed to improve understanding of potentially modifiable risk factors for both caries and periodontal diseases, specifically in relation to:
    - Hypo-salivation and reduced salivary flow
    - Smoking / Tobacco use
    - Carbohydrate (sucrose and starches) impacts upon biological pathways to disease, specifically exploring the effects of sugar frequency/amount in relation to caries and periodontal diseases
    - Micronutrient deficiencies and their impact upon disease initiation and progression, specifically in relation to vitamin’s C, D and K, B6, B12, docohexanoic acid, ecosapentanoic acid and trace elements and minerals such as magnesium, calcium and phosphate
    - Longitudinal controlled studies focusing on the influence of dietary fats and fat types, and proteins on caries and periodontal diseases
    - Multi-centre intervention studies analysing the efficacy of micronutrient supplementation and carbohydrate restriction upon disease status
    - Metabolic syndrome (including diabetes and obesity) and the impact of its management upon periodontal diseases and caries

- Conduct studies on caries in adults to better understand what the most important acquired risk factors are and whether their modification (where feasible) improves caries outcomes
- Conduct further high quality research in the elderly, in order to ascertain whether risk factors for periodontal diseases change across the life course. Also, to elucidate strategies for risk factor reduction in frail older people and those living in care homes who lack independence;
- Investigate the effects of sugar through mechanisms other than those impacting on the biofilm upon periodontal diseases (inflammatory response)
- Monitor changes in dental disease prevalence subsequent to the introduction of new dietary guidelines, such as those recommended by the WHO;
- Evaluate whether caries and/or periodontal diseases can be managed through diet changes with the help of motivational interviewing;
- Determine the efficacy of other dietary interventions such as functional foods, pro/prebiotics, and sugar alcohols in caries and/or periodontal disease prevention/management.

Recommendations for the Dental Team

- Routinely question patients about a family history of periodontal diseases and caries;
- Modern preventive practice should focus on the identification of risk in individuals using validated risk assessment tools;
- Routinely include questions on dietary behaviour or habits in order to identify risk in individuals/groups;
- Nutritional assessment should always be performed when there is disease activity;
- Provide advice and support for a healthy diet according to national dietary guidelines;
- Encourage sugar ingestion cessation for individuals with active caries and/or gingival bleeding, or as a minimum reduce frequency of sugar intake to mealtimes;
- Advise on dietary starch reduction for individuals with root caries;
- Increase awareness of importance of vitamin D and antioxidant micronutrients through natural dietary sources, especially in the elderly;
- Refer to a dietician or general medical practitioner when necessary;
- Engage the entire oral healthcare team in smoking cessation advice and support, and refer where necessary to specialist services;
- Engage in discussions on weight loss from the perspective of oral diseases like periodontitis;
- Encourage adherence to glycaemic control regimes in diabetes patients, from a periodontal health perspective;

- Routinely examine intra-oral saliva production/moisture levels and consider fluoride supplements and/or saliva substitutes for patients with reduced salivary flow.

Recommendations for Non-Dental Healthcare Professionals

There are a number of groups of Non-Dental Healthcare Professionals who urgently need to know about periodontal diseases and caries that they are distinct diseases with different pathobiological mechanisms and to understand the on-going balance between risk factors (e.g. smoking), protective factors (e.g. fluoride in caries, high levels of oral hygiene in periodontal diseases) and pathological factors. These determine whether health is maintained, or whether disease will be initiated and subsequently progress. These groups include physicians (from paediatricians to general practitioners, to geriatricians), Nurses (from public health nurses to community "health visitors", to those working in oncology and geriatric settings), Pharmacists (from the standpoint of a general awareness of the cariogenicity associated with salivary depletion as well as an awareness of the dangers medicines with added sugar, and the importance of smoking cessation to periodontal diseases), Dietitians including all those involved with diet and nutrition, Nursery care workers and Midwives working in well baby clinics.

Recommendations for Caries

These groups must appreciate that: 1) dental caries is a biofilm-mediated, sugar-driven, multi-factorial, dynamic disease resulting over time in the episodic demineralisation of dental hard tissues, 2) caries risk in individuals and groups will vary considerably, 3) the caries process produces lesions of a range of extent and severity - each stage of which can be either active or inactive, 4) that modification of lifestyle, dietary and behavioural factors may influence both new disease and progression of existing lesions which may, at the early stages, be arrested or reversed. They should know that a multifaceted approach minimising all the pathological factors while focussing on diet and self-care including the frequent use of a toothbrush with a fluoride toothpaste is most likely to be effective in controlling this largely preventable disease.

They should be aware that from a caries standpoint, aside from the common risk factors associated with both caries and obesity and links to hypo-salivation and maternal smoking, robust evidence for direct links to systemic disease and specific genetic factors is absent.

Wherever possible, they should provide interventions and advice which is meaningful at an individual level and which link benefits for caries, periodontal diseases and systemic health.

Specific recommendations for caries are:

- Recommend drug substitution where reduced salivary flow rate is a complication of a specific medication.

Recommendations for Periodontal Diseases

There are different forms of periodontal disease (gum disease) but the most ubiquitous are gingivitis and periodontitis. Gingivitis is a necessary pre-requisite for periodontitis and whilst not all cases of gingivitis will progress to periodontitis, managing the former is a vital primary preventive strategy for preventing the latter. Periodontitis causes tooth loss if left untreated. In its more severe forms periodontitis is independently associated with higher mortality rates, likely due to robust evidence that it is associated with and increased risk for atherogenic cardiovascular diseases, diabetes control and related complications. Other key facts include: 1) having periodontitis does not necessarily mean that someone has neglected proper oral self-care. Susceptibility varies and the most highly susceptible individuals may acquire the disease even with relatively good oral hygiene; 2) risk to periodontitis has a strong heritability, but lifestyle and environmental factors and behaviours are key to determining whether disease develops or progresses; 3) periodontitis is treatable to the extent that teeth can be retained for life, but early diagnosis is vital and the disease can start in adolescence or in later teenage years; 4) bleeding gums are NOT normal and the appearance of blood in saliva following toothbrushing is not normal and for this a dental care professional should be consulted to further investigate this and adequate treatment should be provided; 5) whilst periodontitis is not a communicable disease, the bacteria that initiate the disease can be transferred between individuals and, if transferred to a susceptible individual, their immune response may start to trigger the signs and symptoms of periodontitis; 6) periodontitis should be regarded as a “sign post” condition, that may indicate malnutrition or that a patient may have an underlying chronic non-communicable disease (e.g. undiagnosed diabetes) and the advice of a dental care professional should be sought.

Specific recommendations for periodontal diseases are:

- Encourage patients with bleeding gums or bad breath or any looseness of teeth, or with gaps appearing between teeth to visit a dental care professional for an examination and diagnosis;
- Encourage everyone with signs of periodontal disease to clean between their teeth once daily, as directed by a dental are professional;
- Ensure that patients realise that unhealthy gums can be associated with other general health issues and that the mouth is a vital part of the body and not a separate organ;
- Encourage care workers to seek advice in how to implement individual oral hygiene in care home residents.

Specific recommendations for caries and periodontal diseases are:

- Encourage mothers to instil twice daily tooth brushing in their children from the moment the first baby tooth appears Encourage everyone to brush their teeth twice daily with a fluoridated toothpaste and for those with a full dentition timed for at least 2 minutes each session;
- Encourage nursing mothers and other child carer's to employ sugar-free drinks from birth;
- Increase awareness of the risk of diets high in sugar and sugar-containing medication for caries and periodontal diseases, especially in the very young and in the elderly;
- Encourage all to limit frequency of sugar intake (ideally to mealtimes) and amount of intake;
- Encourage the use of sugar free drinks, mints and chewing gums;
- Include oral health (caries and periodontal diseases) into medical preventive programmes, in particular in relation to diabetes, obesity, metabolic syndrome and cardiovascular disease (periodontal diseases);
- Increase knowledge about the impact of diets high in sugars and low in antioxidant micronutrients on oral health in nursing homes;

Recommendations for Public Health and Policy Makers

Periodontal diseases and caries are ubiquitous, underlie virtually all tooth loss and are largely preventable. Retaining healthy teeth improves nutritional status, reduces the risk of general health consequences of these oral diseases, helps reduce health inequalities, has significant positive health economic impacts and improves quality of life and general wellbeing. Public policy should encourage: 1) all nursing mothers to have their baby's entered into regular dental care pathways; 2) all care homes to develop mechanisms and processes for maintaining the oral health status of their residents; 3) immediately develop remuneration approaches that encourage prevention and an individually tailored plan of care rather than intervention in dental contracts and payment systems; 4) embed risk assessment and risk driven care pathways into clinical care; 5) develop strategies to address oral health inequalities in areas of high socio-economic need; 6) lobby and influence nutritional policies to reduce sugar containing snacks and foods in public areas, educational and recreational environments; 7) lobby to reduce the costs of healthy snacks, fruits and vegetables high in micronutrients.

Wherever possible, policy interventions should be meaningful at a population / individual level and should be designed to combine benefits for caries, periodontal diseases and systemic health.

Recommendations for Caries

It should be understood by Public Health agencies and Policy Makers that: 1) dental caries is a biofilm-mediated, sugar-driven, multi-factorial, dynamic disease resulting over time in the episodic demineralisation of dental hard tissues, 2) the on-going balance between protective and pathological factors will determine whether health is

maintained, or whether caries lesions will be initiated and then progress, 3) adequate use of fluoride is a condition *sine qua non* for caries prevention, and 4) that modification of lifestyle, dietary and behavioural factors may influence both new disease and progression of existing lesions which may, at the early stages, be arrested or reversed.

To combat this ubiquitous disease which continues to represent a significant health and economic burden across the life-course, Agencies and Governments should put in place a locally appropriate combination of aligned upstream, mid-stream and downstream policies and activities aimed at caries prevention and control. Comprehensive implementation of the recent WHO guidelines on sugar consumption should be delivered and combined with other fluoride-related interventions. The focus should be on reducing the risk for caries initiation and progression across populations and risk groups. For example, in some countries taxes on sugar and beverages with added sugar are being introduced and show some promise.

Effective education is also needed to update the public, patients, health professionals, healthcare providers and decision makers regarding the dynamic and initially reversible nature of the caries process. They also need to know that both primary and secondary preventive interventions are available to reduce the risk of new caries and caries progression.

Specific recommendations for caries are:

- Ensure foods and drinks distributed at schools follow the latest health recommendations;
- Promote absence of processed foods for pre-school and school children.

Recommendations for Periodontal Diseases

Public Health agencies and Policy Makers should ensure that periodontal screening becomes a mandatory component of the oral health examination and consider mandatory reporting of periodontal screening to appropriate local commissioning bodies. It is important to recognise that the evidence base for periodontal disease risk factors has strengthened and smoking cessation and glycaemic control in non-diabetes as well as diabetes patients are strong risk factors for developing periodontitis. There is a need to focus limited resources on 1) preventive strategies for periodontal diseases and remuneration systems that demonstrate their uptake and implementation; 2) behaviour change for prevention and reinforcement of good lifestyle practices, employing the wider oral health workforce; 3) developing educational programmes for antenatal midwifery classes, health visitors, teachers at primary and secondary schools, pharmacists, general nurses, and also for care home workers; 4) develop public awareness campaigns about gum diseases that are independent from the oral healthcare industry.

Specific recommendations for periodontal diseases are:

- Take responsibility for developing public health campaigns educating the public about gum disease;

- Develop education packages to become embedded in key stage health services that span the life course, from antenatal (midwifery) clinics to health visitors, to primary schools and secondary schools and care homes;
- Lobby to recognise oral health as a vital and integral aspect of general health and wellbeing;
- Ensure messaging about reducing sugar consumption is applied to gum diseases as well as dental caries, by flagging that sugar causes inflammation.

Specific recommendations for caries and periodontal diseases are:

- Include prevention and the development of individually tailored oral care plans in the reimbursement system of countries
- Ensure remuneration systems focus upon risk-based prevention and no longer solely upon remuneration by intervention;
- Seek to provide a free dental check-up for key stages in life, using “touch points” such as for example at 2 years, 5-years, 12 years, 26-years, 40 years and 70-years of age;
- Carry out counselling on dietary sources of vitamin D to pregnant women and parents of infants and children;
- Carry out counselling on dietary sources of antioxidant micronutrients, such as vitamin C and vitamin D.

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